PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION See Form PCT/IPEA/416	
PC-21017792		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE2004/001955	22.12.2004	22.12.2003
International Patent Classification (IPC) or national classification and IPC		
See Supplemental Box		
Applicant		
BIOFOL AB et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))
      _____, containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20.10.2005	22.12.2005
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. +46 8 667 72 88	Authorized officer Ida Christensen/MP Telephone No. +46 8 782 25 00

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of: Cover sheet

INTERNATIONAL PATENT CLASSIFICATION (IPC):

A61K 31/519 (2006.01)
A61P 35/00 (2006.01)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE2004/001955

Box No. I Basis of the report

1. With regard to the **language**, this report is based on:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____ ,
which is the language of a translation furnished for the purposes of:

- ☐ international search (Rules 12.3(a) and 23.1(b))
- ☐ publication of the international application (Rule 12.4(a))
- ☐ international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

☒ the international application as originally filed/furnished

☐ the description:

pages _____ as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ the claims:

pages _____ as originally filed/furnished
pages* _____ as amended (together with any statement) under Article 19
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ the drawings:

pages _____ as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing *(specify)*: _____
- ☐ any table(s) related to the sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing *(specify)*: _____
- ☐ any table(s) related to the sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE2004/001955

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 17-23

because:

☒ the said international application, or the said claims Nos. 17-23 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See PCT Rule 67.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for said claims Nos. _____

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in the Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE2004/001955

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-16	YES
	Claims		NO
Inventive step (IS)	Claims	1-16	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-16	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The present application relates to the use of tetrahydrofolate (FH4), methylene-tetrahydrofolate (CH2FH4) and/or methyl-tetrahydrofolate (CH3FH4), and at least one multi-targeting antifolate for the manufacture of a pharmaceutical composition for the treatment of cancer. The aim is to provide a more efficient method of reducing the toxic side-effects of multi-targeting antifolates while maintaining (or improving) the anti-tumour action of said drugs.

Reference will be made to the following documents cited in the International Search Report:

D1) Seminars in Oncology, 29(2), suppl 5: 3-7 (2002), Calvert H.
D2) WO 9117660
D3) Molecular Cancer Therapeutics, 1: 545-552 (2002), Niyikiza C. et al.
D4) Anticancer Research, 18(5A): 3235-3239 (1998), Worzalla J F et al.

Through D1 it is known that the toxic effects of antifolates, such as the multi-targeting antifolate pemetrexed, are related to relative folate deficiency in some cancer patients. Nutritional supplementation of folic acid led to a marked reduction in toxicity and the abolition of treatment-related deaths with apparent preservation of anticancer activity. D1 argues that it is reasonable to expect that patients with poor folate status would be more likely to suffer toxicity because natural folates can compete with antifolates for cellular uptake and polyglutamation and potentially at the target enzyme site.

.../...

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of: Box V

Pemetrexed is a potent inhibitor of thymidylate synthase (TS), glycinamide ribonucleotide formyltransferase and dihydrofolate reductase in vitro (see pages 4-6).

The invention according to claims 1-16 is novel.

D1 is considered to represent the closest prior art. The technical feature distinguishing the subject-matter of claim 1 from what is disclosed in D1 is that FH4, CH2FH4 or CH3FH4 is administered instead of folic acid in combination with a multi-targeting antifolate.

In the present application, it is stated that many metabolic steps are required in order to achieve CH2FH4, which is one of the active substances of folic acid metabolism. It is shown that administration of CH2FH4 leads to a higher tissue concentration of CH2FH4 than the tissue concentration of folic acid obtained by administering folic acid, which indicates that it is more efficient to directly administer CH2FH4 instead of folic acid. The technical effect of the distinguishing feature of claim 1 is that the toxicity of the multi-targeting antifolate is reduced while the anti-tumour effect is maintained (or even improved). Consequently, with the background of D1, the problem is to develop an alternative, more efficient method of achieving reduced toxicity of multi-targeting antifolates.

D2 discloses a method for treating cancer by administration of CH2FH4 or FH4 in combination with 5-fluorouracil (5-FU). D2 also describes a method for reducing the toxicity of an antifolate drug by use of CH2FH4 or FH4 (see page 11, lines 14-19). The antimetabolite drug used in D2 is 5-FU, which is a single enzyme targeting antifolate, which acts by inhibition or abrogation of TS activity through formation of the specific metabolite fluorodeoxyuridylate (FdUMP). CH2FH4 is a normal intracellular metabolite of folic acid and is a substrate for at least four different enzymes. CH2FH4 must be present in high concentration for inhibition of TS to occur and it is the best folate form for formation of TS-FdUMP-folate ternary complexes. In order to maximise the inhibition of TS, CH2FH4 or FH4 is administered instead of folinic acid (page 3, line 1 - page 7, line 32).

.../.../...

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of: box V

As mentioned in D1, inhibition of TS is also one of the therapeutic mechanisms obtained by the multi-targeting antifolate drug pemetrexed. However, according to the Applicant, multi-targeting antifolates are significantly different from the group of compounds to which single enzyme targeting antifolates belong. D2 could only be considered relevant on the assumption that toxic side-effects caused by single enzyme targeting antifolates can be placed on a level with side-effects caused by multi-targeting antifolates, which according to the Applicant is not self-evident.

It is therefore not considered to be obvious for a person skilled in the art to use the teachings of D2 together with prior-art as specified in D1 in order to achieve a more efficient method of reducing toxicity of multi-targeting antifolates by use of CH2FH4 or FH4 instead of folic acid according to the claimed invention.

Accordingly, the subject-matter of claim 1 involves an inventive step.

For the same reasons, the subject-matter of claims 2-16 is considered to involve an inventive step.

The subject-matter of claims 1-16 fulfils the requirement of industrial applicability.

The documents D3 and D4 pertain to folic acid supplementation to cancer patients in order to reduce the toxic effects of multi-targeting antifolates such as pemetrexed and lometrexol. D3 and D4 are considered to represent prior art.